D- 9007/LINURON SR 5-25-84

Attachment B

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
May 25, 1984

OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: Review of Rat and Mouse Data from the Dupont Chemical Company for the Carcinogenicity of Linuron

FROM: Robert E. McGaughy R E McGaughy
Acting Technical Director
Carcinogen Assessment Group (RD-689)

TO: Ann Barton
Acting Director
Hazard Evaluation Division (TS-769)

THRU: Elizabeth L. Anderson E.L.A. for E.L.A.
Director
Office of Health and Environmental Assessment (RD-689)

Two members of the Carcinogen Assessment Group (CAG), Drs. Bernard H. Haberman and Chao W. Chen, have reviewed the available data on linuron and have prepared the attached report dealing with the qualitative and quantitative assessment of the carcinogenicity of linuron.

In January we circulated a draft for internal Office of Health and Environmental Assessment and Hazard Evaluation Division review. We have addressed the comments received from our internal review. Because we did not receive comments from your office, we assume that the report meet your needs, and we are hereby transmitting it to you.

Please let me know if we can be of any further assistance.

Attachment

cc: John A. Moore (TS-788)
Edwin L. Johnson (TS-766)
Amy Rispin (TS-769)
Kyle Barbehenn (TS-769) ✓
Ingrid Sunzenauer (TS-794)
Therese Murtagh (TS-757c)

DRL

Attachment to D-9004A

April 30, 1984

THE CARCINOGEN ASSESSMENT GROUP'S REVIEW OF RAT AND MOUSE DATA FROM THE DUPONT CHEMICAL COMPANY FOR THE CARCINOGENICITY OF LINURON

Prepared by

Chao W. Chen, Ph.D.
Bernard H. Haberman, D.V.M., M.S.

Participating Members

Roy E. Albert, M.D. (Chairman)
David L. Bayliss, M.S.
Steven Bayard, Ph.D.
Margaret M.L. Chu, Ph.D.
Herman J. Gibb, B.S., M.P.H.
Sharalingayya B. Hiremath, Ph.D.
Robert E. McGaughy, Ph.D.
Sharm V. Singh, D.V.M., Ph.D.
Todd W. Thorslund, Ph.D.

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United States
Environmental Protection
Agency

OHEA-C-117
April 30, 1984

EPA

Research and Development

REVIEW OF RAT AND MOUSE DATA FROM THE DUPONT CHEMICAL COMPANY FOR THE CARCINOGENICITY OF LINURON

Prepared for

Office of Pesticides and Toxic Substances
Office of Pesticide Programs
Hazard Evaluation Division

Prepared by

Carcinogen Assessment Group
Office of Health and
Environmental Assessment
Washington DC 20460

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REVIEW OF RAT AND MOUSE DATA FROM THE DUPONT CHEMICAL COMPANY FOR THE CARCINOGENICITY OF LINURON

At the request of the Hazard Evaluation Division (HED) of the U.S. Environmental Protection Agency's Office of Pesticide and Toxic Substances, the Carcinogen Assessment Group (CAG) reviewed a summary technical evaluation of rat data prepared by the staff of the Office of Pesticide Programs (OPP) and an initial evaluation of mouse bioassay data developed at the Haskell Laboratory for DuPont Chemical Company.

The qualitative assessment of this review was prepared by Dr. Bernard H. Haberman, and the quantitative assessment was prepared by Dr. Chao. W. Chen.

QUALITATATIVE ASSESSMENT

A summary of the 2-year rat feeding study of linuron conducted by DuPont (1980) was prepared by Dr. James Holder of the HED and submitted to the CAG for review. The CAG agrees that there is a positive interstitial cell (ISC) adenoma response in the testes of male Charles River CD rats. The major data from Dr. Holder's report, presented in Table 1, show a statistically significant increase in the incidence of ISC adenomas in male rats at both 125 and 625 ppm in the diet. The historical control incidence for the incidence of ISC adenomas in this rat strain from five different studies performed at DuPont's Haskell Laboratory during the same time period as the 1980 rat study averaged about 17% (range was 8.6 to 20.3%). This historical data was presented in a letter from Dr. R. Everett, DuPont, to Dr. J. Holder, EPA (June 10, 1982).

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TABLE 1. INCIDENCE OF INTERSTITIAL CELL ADENOMAS OF THE TESTES IN MALE CHARLES RIVER CD RATS FED LINURON FOR 2 YEARS
(adapted from Holder September 15, 1982)

Dose (ppm)	No. of rats in 2-year test*	Incidence (no. of rats with tumors/ no. of rats examined)
0	70	4/70 (5.7%)
50	69	9/69 (13.0%)
125	70	20/70 (28.6%) $P = 2.7 \times 10^{-4}$†
625	70	37/70 (52.9%) $P = 2.3 \times 10^{-10}$†

*These numbers do not include the 10 rats/group sacrificed at one year, since none of these rats had ISC adenomas.
†P values calculated by the Fisher's Exact Test.

A chronic study of mice fed linuron (Haskell Laboratory Report No. 758-82) was also reviewed. Linuron (INZ-326) was fed to male and female Charles River CD-1 mice for 24 months at levels of 0, 50, 150, and 1500 ppm in the diet. The dose rates for the three linuron-treated groups are reported to be 12, 35, and 455 mg/kg/day. These values could be somewhat inflated because of the high reported food consumption (about twice the normal values), probably a result of excessive food spillage during the first 32 weeks. Eight groups of 80 mice each were used in this study. All animals were subjected to both gross and microscopic pathological examination when either terminal sacrifice was reached (24 months) or when found dead or sacrificed in extremis. During the study, selected animals were used for hematological examination.

Survival data indicated no real differences between control and treated groups. At the 1500 ppm dose, mean body weight and mean body weight gain were decreased in both male and female mice throughout the experiment. The values

of methemoglobin were increased in treated mice of both sexes; this increase was related to compound administration. The mean absolute and relative liver weights were increased in female mice in the 1500 ppm dose group.

Microscopic examination of the tissues and organs of these mice indicated that abnormalities were present in the livers and spleens of male and female mice; these abnormalities appeared to be related to compound administration. Slightly increased incidences of hemosiderosis of the spleen were reported for both male and female mice in the 1500 ppm dose group. Compound-related effects in the liver included hepatocytomegaly, hepatocellular cytoplasmic alteration, hepatocellular vacuolization, hemorrhage, and necrosis. A statistically significant increase in the incidence of hepatocellular adenomas was observed at the highest dose group (1500 ppm) in female mice, and border-line statistical significance was reached for hepatocellular adenomas in the lowest dose group only (50 ppm) in male mice (Table 2). Also, no significant increases were presented for hepatocellular carcinomas only in either sex at any dosage.

Dr. John Fowle of the Reproductive Effects Assessment Group (REAG) stated that the data are inadequate for assessing the mutagenic potential of linuron because of the limited tests conducted (memo to Dr. R. McGaughy, May 13, 1983).

Based on the criteria of the International Agency for Research on Cancer (IARC), one can thus conclude that the weight-of-evidence for the carcinogenicity of linuron is very limited for animals and is in Group 3 overall, because of the absence of any human data, a positive response for benign interstitial cell adenomas of the testes in male Charles River CD rats, and benign hepatocellular adenomas female Charles River CD-1 mice. A mechanism of oncogenesis cannot be inferred for linuron with the present data. Since a mechanism(s) is (are) not known, it is a moot point to question how such a mechanism(s) might affect the assessment of oncongenic risks at appropriate

TABLE 2. INCIDENCE OF LIVER TUMORS IN MALE AND FEMALE CHARLES RIVER CD-1 MICE FED LINURON FOR 24 MONTHS
(adapted from DuPont Chemical Company 1982)

Diagnoses	Doses			
	0 ppm	50 ppm	150 ppm	1500 ppm
		Males		
Hepatocellular Adenoma (HA)	9/79(11.4%)	18/80(22.5%) P = 0.048*	10/80(12.5%)	16/78(20.5%)
Hepatocellular Carcinoma (HC)	4/79(5.1%)	3/80(3.8%)	3/80(3.8%)	2/78(2.6%)
Combined (HA and HC)	13/79(16.5%)	21/80(26.3%)	13/80(16.3%)	18/78(23.1%)
		Females		
Hepatocellular Adenoma (HA)	5/79(6.3%)	6/79(7.6%)	8/76(10.5%)	20/80(25%) P = 0.001*
Hepatocellular Carcinoma (HC)	1/79(1.3%)	1/79(1.3%)	3/76(3.9%)	2/80(2.5%)
Combined (HA and HC)	6/79(7.6%)	7/79(8.9%)	11/76(14.5%)	22/80(27.5%) P = 8.2×10^{-4}*

*P values calculated by the Fisher's Exact Test.

levels of human exposure. Further studies that might elucidate some mechanism(s) for the carcinogenicity of linuron should include long-term carcinogenicity studies in animals with simultaneous hormonal determinations during these studies.

QUANTITATIVE ASSESSMENT

The incidence rates of hepatocellular adenomas and carcinomas combined in female mice (Table 2) are used to estimate an upper limit for the carcinogenic potency of linuron. An underestimation of the potency might result because of the unusually high reported food consumption; although the actual potency might be twice the estimates presented below, there are no data in the report which would allow a more accurate calculation. Table 3 presents potency estimates calculated by using the multistage model for the low-dose extrapolation and two different assumptions for the equivalent doses between mice and humans. The 95% upper-bound estimate of the linear component, $q_1^* = 9.8 \times 10^{-3}/(mg/kg/day)$, is calculated using the assumption that the equivalent dose betweeen species is milligrams per body surface area. The value q_1^* is used by CAG to represent the carcinogenic potency of an agent. For linuron, the maximum likelihood estimate, $6.1 \times 10^{-3}/(mg/kg/day)$, is only slightly smaller than the upper-bound estimate, $q_1^* = 9.8 \times 10^{-3}/(mg/kg/day)$. The carcinogenic potency index (2×10^0), which is calculated by multiplying q_1^* by the molecular weight (249), and is used by the CAG to rank the carcinogens in terms of potency, places linuron in the lower fourth quartile among 54 suspect carcinogens evaluated by the CAG.

Because of the uncertainity associated with regarding linuron as a human carcinogen, the cancer potency estimate must be cautiously interpreted. The cancer potency value is "conditional" in that the estimate is only plausible

TABLE 3. ESTIMATES OF THE CARCINOGENIC POTENCY $(mg/kg/day)^{-1}$ FOR LINURON ON THE BASIS OF LIVER TUMORS IN FEMALE MICE

	Equivalent dose rates	
	On the basis of body weight	On the basis of surface area
Maximum likelihood estimate	5.1×10^{-4}	6.1×10^{-3}
95% upper-bound estimate	8.1×10^{-4}	9.8×10^{-3}

Remarks:

1. The maximum likelihood estimates of the parameters for the model $P(d) = 1 - \exp[-(q_1 d + q_2 d^2 + q_3 d^3)]$ are $q_1 = 5.1 \times 10^{-4}$, $q_2 = q_3 = 0$.

2. The body weights are assumed to be 70 kg for humans and 0.04 kg for mice. (For equivalence dose transformation and methodology for risk calculation, see Federal Register, Part V, 45:(231):79316-79379, November 28, 1983.)

if the assumption is made that linuron is probably carcinogenic in humans, the weight-of-evidence for this assumption being very limited. It is important to consider the weight-of-evidence along with the potency estimates in evaluating the potential human health hazards of linuron.

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MEMORANDUM

SUBJECT: Linuron Oncogenic Risk Assessment

TO: Ingrid Sunzenauer, RM
SRB/Registration Division (TS-767)

The oncogenic properties of linuron have been reviewed by the CAG (McGaughy 23 January, 1984) and TOX Branch (Burnam 14 February, 1984). Using NTP criteria, Burnam concluded that the rat study indicated "clear evidence of carcinogenicity". Using IARC criteria for carcinogenicity in humans, CAG concluded that the evidence was very limited. Additionally, I understand that the registrant has research underway that may contribute to a biological judgement regarding the validity of the effects observed in the rat as evidence for the carcinogencity of linuron. In view of these uncertainties, I have calculated oncogenic risks using results from both the rat and mouse studies. This should not be interpreted as putting brackets around the range of risk. If we are to regulate linuron as an oncogen, the rat study provides the best model for assessing risks, as indicated by Burnam. Should it be determined in the future that for biological reasons the results in the rat are inappropriate, the mouse study provides the only remaining basis for regulation.

As recommended by Burnam, I have used the Q1* value of 0.328 as calculated by Litt (7 January, 1983) for the upper 95% confidence limit of oncogenic potency in the rat. For the mouse, I have used the Q1* value of 0.0061 - the Maximum Liklihood Estimate provided by the CAG. This tends to reflect their weight-of-evidence judgement. The risk estimate would be increased by 50% if their estimate of the 95% upper bound were used.

Estimates of exposure to private operators applying linuron to soybeans were provided by Keller (6 April, 1984). Table 1 (attached) indicates the increase in oncogenic risks associated with various levels of protective clothing and assumes the user will be treating a 100 acre field once a year for 30 years over a 70 year liretime. The mixer/loader and applicator risk estimates have been combined on the assumption that, in a small operation, both tasks are performed by the same person. Risks will increase in proportion to acreage treated, e.g. with 100% protection, combined risk for treating 600 acres for 30 years will be 1.7×10^{-5}, using the rat model.

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Risks from dietary exposure (Table 2) have been calculated for three conditions: 1. Using the TMRC from current tolerances, 2. Using the maximum residue expected (MRE) rather than the tolerances (Storherr, 30 March 1984), and 3. Using the MRE multiplied by a rough estimate of percent of crop treated. The last values probably provide the best estimate of dietary risk and could be further refined by additional information from BUD should this be desired. Pending tolerances for lettuce and sugar are not included.

It should be noted that diuron is also registered for use on some critical crops such as asparagus, potatoes and wheat.

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Kyle Barbehenn, Biologist
Science Integration Staff
Hazard Evaluation Division, TS-769

Attachments

cc: Anne Barton
Amy Rispin
Bill Burnam

Table 1

Linuron: Oncogenic Risk to Field workers.

CONDITION	EXPOSURE mg/kg/yr/100A	RELATIVE exposure factor	ADDED RISK (100 A/yr x 30yr) model	
			mouse	rat
No Protection				
Mixer/loader	.095	79	6.9×10^{-7}	3.6×10^{-5}
Applicator	.0045	3.8	3.3×10^{-8}	1.7×10^{-6}
Combined	.10	83	7.2×10^{-7}	3.8×10^{-5}
80% Protection				
Mixer/loader	.022	18	1.6×10^{-7}	8.3×10^{-6}
Applicator	.0018	1.5	1.3×10^{-8}	6.9×10^{-7}
Combined	.024	20	1.7×10^{-7}	9.2×10^{-6}
100% Protection				
Mixer/loader	.006	5	11.3×10^{-8}	2.3×10^{-6}
Applicator	.0012	1	8.7×10^{-9}	4.6×10^{-7}
Combined	.0072	6	5.2×10^{-8}	2.8×10^{-6}

Table 2

Linuron: Oncogenic Risk from Dietary Exposure

Assumption	"TMRC" (mg/day)	INCREASED RISK mouse model	rat model
100% tolerance	0.3248	3.3×10^{-5}	1.2×10^{-3}
MRE	0.0790	7.9×10^{-6}	4.3×10^{-4}
MRE x % treated	0.0027	2.7×10^{-7}	1.5×10^{-5}